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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,211	07/25/2003	Benjamin Frydman	376462001900	4243

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EXAMINER	
FEDOWITZ, MATTHEW L	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/627,211	FRYDMAN ET AL.	
	Examiner	Art Unit	
	Matthew L. Fedowitz	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Pri rity under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 are pending in this action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Han (US 2002/0155999 A1).

Han Claim 1 anticipates claim 1. Han Claim 7 anticipates claim 2. Han Claim 5 anticipates claim 3. Han Claims 2, 9 and paragraph 25 anticipate claims 4, 5, 6 and 7. Han Claims 2, 9 and paragraph 25 also anticipate claim 8 because a generic disclosure of the prior art directed to a recognizable small class of compounds having common properties, which embrace the claimed compound, is anticipatory not withstanding the fact that the claimed compounds are not specifically named. In re Schaumann, 572 F2d 312, 197 USPQ 5 (CCPA 1978). Mesoporphyrin IX is one of fifteen isomers of mesoporphyrin recognized by IUPAC to be in a small class of compounds. Han Claims 3 and 10 anticipate claims 9, 10 and 11. Han Claims 3 and 10 as well as the figure demonstrating the reaction scheme also anticipate claim 12. Han paragraph 42 anticipates claims 13, 14 and 15. Han claims 12 and 14 anticipate claims 16 and 17. Han claim 14 anticipates claim 18 where the onium reagent is diazonium.

Claim Rejections - 35 USC § 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 –11 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the chemotherapeutic agent doxorubicin and the porphyrin mesoporphyrin IX, does not reasonably provide enablement for making and using a porphyrin and a chemotherapeutic agent other than doxorubicin covalently linked with a group other than –NH-C(O)-$(CH_2)_2$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to treat uncontrolled cell proliferation related diseases or to make the diverse compounds claimed commensurate in scope with the instant claims without undue experimentation.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations. In re Wands, 8 USPQ2d 1400 (CAFC). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include but are not limited to:

1. The breadth of the claims;

2. The nature of the invention;

3. The state of the prior art;

4. The level of one of ordinary skill;

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The existence of working examples; and

8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Wands Analysis

1. The Breadth of the Claims.

The breadth of the instant claims are seen to encompass a compound comprising a porphyrin covalently linked to a chemotherapeutic agent. Claim1 is drawn to a porphyrin and a chemotherapeutic agent. The claim reads as a composition since relationship between the compounds indicates that they are attached. Claims 2 and 3, which depend from claim 1, require that the porphyrin and the chemotherapeutic agent be covalently attached, but does not articulate where the covalent linkage is located on the porphyrin or the chemotherapeutic agent, and also does not define the chemotherapeutic agent or the covalent linkage. Claims 4-8 further limit the invention by articulating limitations to the porphyrin. Claims 9 and 10 further limit the invention by articulating classes of chemotherapeutically active agents described functionally and by articulating chemical cores of chemotherapeutically active agents. Claim 11, which depends from claim 2, articulates the identity of the chemotherapeutic and the porphyrin, but does not set forth a specific covalent linkage. Claims 13 and 14 are drawn to the use of the compound of claim 2 to treat uncontrolled cell proliferation and cancer (broadly). Claim 15 is drawn to the use of compounds in claim 10 to treat uncontrolled cell proliferation. Claims 16 and 17 are drawn to

processes for making compounds of claims 2 and 12 respectively, and claim 18, which depends from claim 17, further limits the reagents used in claim 17.

2. The Nature of the Invention.

The nature of the invention relates to porphyrin compounds, processes for making the same and using porphyrins with chemotherapeutic agents to treat uncontrolled cellular proliferation characterized diseases, more specifically cancer. The treatment of diseases requires a host, i.e. an animal, cell line, etc. It is noted that the function of the active agent should be adequately correlated to the disease treatment in a host or cell line. Further, it is known that cancer therapeutics is highly unpredictable (see Katzung pp.881-882) and the current state of use of porphyrins as chemotherapeutic agents is unpredictable as well (see Foye *et al.* pp. 902-904).

3. The State of the Prior Art.

The applicant discloses examples in the specification to demonstrate the ability to synthesize porphyrin compounds where doxorubicin is covalently linked to mesoporphyrin IX via an $-NH-C(O)-(CH_2)_2$ linkage. The showing of an example that synthesizes a single compound does not provide and adequate representation to enable one to synthesize porphyrins linked to a vast number of chemotherapeutic agents in general and as listed in claim 9 commensurate in scope with the instantly claimed invention. As a result of this finding and the lack of adequate guidance or representations in the specification, the applicant has not enabled this aspect of the claimed compounds, processes for using the same or methods for making same broadly. The skilled artisan in this field would not accept the representations set forth in the

instant disclosure as sufficient to enable methods for making and using porphyrin chemical cores broadly, linked via some functionally described covalent linkage to a non-doxorubicin chemotherapeutic agent.

4. The Level of Ordinary Skill

The level of skill is that of one with a doctoral understanding of chemical synthesis and chemotherapeutics.

5. The Level of Predictability in the Art

The synthesis of porphyrin compounds is unpredictable and is limited by the fact that the nature of the porphyrin's chemical cores makes synthesis difficult. Moreover, to subsequently add an agent of vastly diverse structure (i.e. chemotherapeutic agents with diverse core such as nucleotides, taxanes, and anthracycline glycosides), through an undefined covalent linkage compounds this difficulty. There is no art-recognized interchangeability for chemotherapeutics of diverse structure for treating uncontrolled cell proliferation characterized diseases.

6. The Amount of Direction Provided by the Inventor

The applicant has not demonstrated sufficient guidance provided in the form of adequate supporting representations or art recognized correlations in patent or non-patent literature. For example, the applicant only discloses examples of how to synthesize a compound where doxorubicin is covalently linked to mesoporphyrin IX. This does not enable synthesizing porphyrins attached to "other vinca alkaloids," antimicrotubule agents, taxanes, topoisomerase I

or II inhibitors, platinum complexes or nitrogen mustards, nor does it enable the use of such compounds.

7. The Existence of Working Examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to make and use compounds comprising a non-mesoporphyrin IX and non-doxorubicin covalently linked thereto. Applicant's broad claims necessarily require a broad disclosure or guidance in the art to accept the methods for making modified porphyrin compounds and using the same to treat disease commensurate in scope with the instant claims.

8. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

In order for compounds comprising a porphyrin linked to a chemotherapeutic agent, it would be necessary to demonstrate how to make the claimed compounds by providing references that contain directions or examples from which would direct one how to make the claimed compounds. The specification submitted and examples therein do not demonstrate this. Therefore, one of ordinary skill in the art would require a significant amount of experimentation in order to a porphyrin linked to any chemotherapeutic agent.

Claim Rejections - 35 USC § 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 9 use the terms "chemotherapeutic agent" and "porphyrin" and defines the term chemotherapeutic agent in the specification with such terms as antitumor antibiotics, antimicrobule agents, other vinca alkaloids, nitrogen mustards, platinum complexes, folate analogs, purine analogs, adenosine analogs, pyrimidine analogs, substituted ureas, camptothecin analogs, topoisomerase I and II inhibitors and anthracycline antibiotics. The terms "chemotherapeutic agent" and "porphyrin," where not further defined as a covalently linked entity render the claims indefinite. The term "covalent linking group" in the absence of a chemical core, structure, or formula is not distinctly claimed. This lack of distinction renders the claims, which do not particularly point out the identity of the linking group, indefinite. Moreover, in the absence of the specific moieties applicant intends as analogs to the chemical core claimed or distinct language to describe the structural modifications or the chemical names of derivative or analogous instantly claimed, the identity of said derivatives and analogs would be difficult to describe and the metes and bounds of said derivatives and analogs that applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

In addition, the applicant uses the term "crystalline forms" and does not identify the location of the covalent linking group. The term "crystalline form" is indefinite because it fails to specifically state what compounds make up the crystalline form. Also, by not identifying the identity and location of the covalent linking group it is indefinite as to where and how a porphyrin compound is linked to a chemotherapeutic component covalently.

Claims 3, 7, 8, 10, 11, 12, 14, 17 and 18 are also rejected under 35 U.S.C. 112, second paragraph, because claims, which depend from an indefinite claim, are also indefinite because these claims fail to obviate the rejections of the claims from which they depend.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew L. Fedowitz whose telephone number is (571) 272-3105 and can be reached between 8:30am-5:00pm (EST) M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Mr. James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew L. Fedowitz, Pharm.D., J.D.
December 6, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623